REMARKS

Amendment to the Claims

Claim 1 has been amended to correct a typographical error.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-5, 8-11, 15/1, 15/2, 15/3, 15/4, 15/5, 15/8, 15/9, 15/10, and 15/11 were rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,514,378 to Mikos ("Mikos") in view of U.S. Patent No. 3,514,791 to Sparks ("Sparks") or U.S. Patent No. 4,795,459 to Jauregui ("Jauregui"). Claims 12-14, 15/12, 15/13, and 15/14 were rejected as obvious over Mikos in view of Sparks or Jauregui and further in view of U. S. Patent No. 5,709,854 to Griffith-Cima, et al. ("Griffith"). Claims 1-5 and 8-15 were rejected as obvious over Sparks in view of Mikos or Griffith and in view of either Jauregui or U. S. Patent No. 4,916,193 to Tang, et al. ("Tang"). Applicants respectfully traverse these rejections.

The Legal Standard

The starting point for any such analysis must be the Supreme Court's decision in *KSR*, which refocuses the determination of whether a claimed invention is obvious back to the process the Court had defined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id.* at 36.

In the chemical arts, where compounds are so similar as to create an expectation that the claimed new compound would have similar properties as the prior art compounds, the Federal Circuit also has upheld a finding that the claimed invention is not patentable. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007). However, when the prior art disclosed a broad selection of compounds that might have been potential candidates for further investigation, the lack of sufficient guidance and predictability to select the compound at issue supported a finding of nonobviousness. *Takeda Chem. Indus. Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359-60 (Fed. Cir. 2007), *petition for cert. filed*, 76 U.S.L.W. 3374 (U.S. Dec. 20, 2007) (No. 07-838); *see also In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007) (remanding to the Board, noting that despite close similarity of the claimed invention and prior art, rebuttal evidence to which the Board gave inadequate consideration showed unexpected results, a teaching away from appellant's invention and a long felt but unmet need).

Even where the prior art suggests or motivates an inventor to develop the composition or process at issue, the Federal Circuit continues to recognize that there is a critical question under 35 U.S.C. § 103 as to whether the combined teachings of the prior art "would have given rise to a reasonable expectation of success" in achieving what is claimed. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007), *petition for cert. filed*, 76 U.S.L.W. 3393 (U.S. Jan. 2, 2008) (No. 07-888). There, the inventors merely used routine research methods to prove what was already believed to be the case and had not made a patentable invention. *Id.* at 1363-64. However, the court noted that a different case is presented if all the prior art suggested was to explore a general approach and gave only general guidance as to the particular form of the claimed invention or how to achieve it. *Id.* at 1364-65 (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), and *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d

1157, 1166-67 (Fed. Cir. 2006), as continuing to provide useful guidance in determining whether the expectation of success from a line of inquiry found in prior art is so great as to make a resulting invention obvious).

The most recent case in which the Federal Circuit applies an obviousness analysis post-*KSR* is Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd, 533 F.3d 1353 (Fed. Cir. 2008) ("*Eisai*"). In that case the court affirmed a summary judgment for the patent holder as to the validity and enforceability of a patent claiming rabeprazole and its salts. In *Eisai* the Federal Circuit also observed that, when market pressure to solve a problem or a design need is evident, whether there were a finite number of identified, predictable solutions will turn on the evidence available to a person of skill when the invention was made. As the Federal Circuit explains in this opinion, *KSR* assumes there is a starting reference point or points in the prior art, before the invention was made, from which a skilled artisan might identify a problem and pursue potential solutions. *KSR* then presupposes that the record up to the time of the invention would give some reasons within the knowledge of one of skilled in the art to make particular modifications to the prior art to achieve the claimed invention. Finally, *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions. The Federal Circuit cites its recent decision in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), for elaborating that this latter concept embraces an "easily traversed, small and finite number of alternatives . . . ." Where the art is unpredictable, this element of "identified, predictable solutions" "may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai, supra.* Considering all of these factors, the Federal Circuit in

Eisai affirmed summary judgment that the patent claiming rabeprazole was not an obvious modification of a prior art compound.

Analysis

As the discussion above indicates, obviousness is not determined in a vacuum based solely on the prior art. One must determine who is one of ordinary skill in the art and what is the problem to be solved, as well as what is the closest art.

In this case, one of ordinary skill in the art is a PhD or MD with extensive experience in growing of tissues.

As of the priority date of this application, the prior art makes clear that a few tissues had been grown on fibrous or sponge like polymeric matrices. All were amorphous tissue, such as liver or sheets of skin, or connective tissue, such as fibrous tissue.

None of these tissues were under a high degree of stress and strain although such tissues had been included in the lists of materials to be made using the fibrous matrices formed of natural or synthetic polymers.

The problem with heart valves, heart leaflets, and blood vessels is that they operate in a very dynamic system - tremendous stress and strain are present at all times. Therefore any construct must be able to withstand the stress and strain until the material degrades and is completely replaced by the new tissue, which must form under physiological conditions (either in the body or in a suitable bioreactor) which provides the necessary strain and stress on the growing tissue.

None of the prior art recognizes the need for a construct which withstands stress and strain, as required by all of the pending claims.

(1) each claimed element, specifically forming the matrix in the shape of a cell-matrix construct comprising a fibrous matrix in the shape of a heart valve or heart valve leaflet.

(2) a reasonable expectation that if one did provide such a matrix, that the cells would attach to and proliferate within the matrix to form a **functional** structure.

The Scope and Content of the Prior Art

The prior art cited by the examiner fails to disclose or provide:

Mikos

Mikos discloses biocompatible porous polymer membranes prepared by dispersing salt particles in a biocompatible polymer solution. Mikos discloses that a three dimensional structure can be manufactured from the membranes. The resulting three-dimensional foam or shape is a porous, biocompatible matrix to which cultured cells can attach and proliferate, and can be used for organ transplant or reconstructive surgery (Mikos, column 3, lines 25-45).

Sparks

Sparks describes a die into which is placed a Dacron mesh secured to a stainless steel supporting ring (see column 5, lines 18-24). The die consists of a tube and mandrel (col. 3, lines 29-31). The die may be seeded with cells to make special parts, periosteal cells being used to make bone and epithelial cells being used to make epithelial tissue (abstract). Figures 6-12 illustrate a die for growing a tricuspid heart valve. Sparks further discloses that natural body processes produce the necessary connective tissue to fill the die cavity and form the valve graft (see column 2, lines 27-32 and column 5, lines 32-36).

Sparks is similar to Mikos in that it provides only a stationary support structure, but fails to provide a structure that can also function as a heart or heart valve when seeded with cells. It is also clearly different in not forming a matrix into which cells are seeded and proliferate, but rather that any cells on sit on the surface of the mesh.

Griffith

Griffith discloses a cell-polymeric solution which is injected into an animal where the polymer crosslinks to form a polymeric hydrogel containing dispersed cells and the cells form new tissue in the animal. The hydrogel solution containing the cells can be injected directly into a patient where it hardens into a matrix having cells dispersed therein, or the hydrogel is poured into a mold having a desired anatomical shape, then hardened, which can be implanted into a patient (Griffith, column 1, lines 42-61).

Jauregui

Jauregui discloses an implantable prosthetic device made of biocompatible polymer and having a substantially continuous layer of autologous living cells attached via oligosaccharide-lectin recognition linkages (abstract). The polymer is Teflon, Dacron, polyurethane or a polymer of a compound from the Krebs Cycle (Jauregui, col. 1, lines 50-56). The surfaces of the polymer are processed to provide COOH or NH2 groups for covalently attaching lectins which are used to attach endothelial cells to the prosthetic device.

Tang

Tang discloses totally or partially bioabsorbable devices capable of degrading into biologically innocuous components.

Analysis as to Level of Skill and Knowledge in the Art; Differences with the Art

There is a high level of skill in the field of tissue engineering, but at the time this application was originally filed, May 19, 1995, more than ten years ago, there had been little clinical reduction to practice and there was a great deal of unpredictability. As stated in Mol, et al., *Circulation*, 114(Suppl 1):152-158 (2006) ("Mol") and Schmidt, et al., *Swiss Med Wkly*,135:618-23 (2005) ("Schmidt") (copies of which are attached), 'the first milestone in heart

valve tissue engineering was the successful replacement of a single pulmonary valve leaflet by a tissue engineered autologous leaflet (see Schmidt, first page, right col.) or "the first successful replacement of a single pulmonary valve leaflet with a tissue engineered equivalent, based on a synthetic biodegradable scaffold, was demonstrated in lambs in 1995" citing to studies by inventors in this application. Thus, although tissue engineering tools were available at the time of filing of this application, successful construction of a functional heart valve had been elusive. Most importantly, the first actual reduction to practice, recognized by those in the field, was by the inventors of this application, using the claimed technology.

The differences between the claimed invention and the prior art

Claims 1-5, 8-11, 15/1, 15/2, 15/3, 15/4, 15/5, 15/8, 15/9, 15/10, and 15/11 are not obvious over Mikos in view Sparks or Jauregui.

The Claims

The claims define a method of making a cell-matrix construct for use as a heart valve or heart leaflet comprising implanting into an animal a cell-matrix construct comprising

a fibrous matrix in the shape of a heart valve or heart valve leaflet,

wherein the matrix is formed of a biocompatible, biodegradable polymer

having seeded therein cells selected from the group consisting of endothelial cell, myofibroblasts, skeletal, vascular smooth muscle cells, myocytes, fibromyoblasts and ectodermal cells,

wherein the cell-matrix construct can withstand repeated stress and strain.

The Examiner acknowledged that Mikos does not disclose every element of the claims. Mikos does not disclose matrices preshaped in the form of a heart valve, not does Mikos disclose matrices having a particular function.

According to the Examiner, the missing disclosure of the matrix to be in the form of a heart valve or valve leaflet in Mikos is provided by Vacanti, et al., *J. Pediatric Surgery* 23(1):3-9 (1988) ("Vacanti 1") cited in Mikos (at col. 2, lines 15+). This is incorrect. Mikos states (col. 2, lines 28-35) "Moreover, they (i.e. Vancati 1) recognized the advantage of using synthetic biodegradable polymer substrates to form a scaffold that *mimics its natural counterpart*, **the ECM of the body**, serving both a physical support and an adhesive support for parenchymal cells…". The ECM of the body is not shaped like a heart valve or valve leaflet, thus, relying on this disclosure as providing the teaching of preshaped constructs having the shape of a heart valve or valve leaflet is mischaracterizing the disclosure in Mikos, as well as the disclosure in Vacanti 1 (a copy of which was attached to the amendment and response filed on May 8, 2007). Moreover, ECM is a stationary matrix (analogous to the mortar around bricks) - it is not subject to continuous stress and strain, conditions that would fracture this material.

Mikos discloses matrices having a particular shape; not function. There is no disclosure that one can form a structure that can move and function as the structure to be replaced, such as a heart. A cartilaginous structure is not functional other than as a support structure. Cartilage does not move repeatedly. It is a hard ***avascular*** support structure. In contrast, a heart valve must move repeatedly, be elastic and flexible, and withstand enormous strain. However, the Examiner cited to Mikos col. 4, lines 49-54 as disclosure relevant to matrices having the desired function of a particular tissue. It is unclear how the Examiner arrived at this conclusion. Mikos discloses how three dimensional structures are formed into a desired shape, and states, "a particular

advantage of the use of the membranes is that polymers with different properties and membranes with different porosities can be used to assemble the structure, much as it occurs in nature" (Mikos, col. 4, lines 51-55). One can assemble a structure as it **occurs** in nature. However, this is not tantamount to assembling a structure to *function as it functions in nature*. This is discussed in Schmidt and Mol- prior to 1995 the art had seen some success in making heart valves as they occur in nature; the challenge was getting them to function accordingly.

As admitted by the Examiner, Mikos is silent about vascular tissue. However, the Examiner asserted that the use of tissue engineering employing both resorbable and nonresorbable polymer scaffolds to replace diseased tissue, including vascular tissue, is known in the art, citing Sparks and Jauregui, and that the fact that these polymers can be molded to mimic the shape of the tissue to be engineered is also known in the art (*citing* Mikos, col. 13+). Jauregui discloses a material having cells seeded on the surface, not within a matrix that forms a functional structure. Mikos discloses a method that involves implanting a *stainless steel die* in an animal. A combination of Mikos with the disclosure in Sparks and Jauregui both of which are relied upon for disclosing vascular tissue, would not arrive at the claimed method.

That some of the general technology and polymers were known may be true, however, making a structure with the requisite mechanical physical and mechanical properties necessary for biological function, especially a structure such as a heart valve, had been a challenge and was neither disclosed by nor predictable at the time this application was filed (see Schmidt and Mol). Claim 1 requires the cell-matrix be able to withstand repeated stress and strain. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years. Mikos is silent about heart valves, and therefore does not disclose or suggest how to

make valves which can withstand repeated stress and strain. None of Sparks or Jauregui makes up for this deficiency.

The Examiner alleged that the resulting tissue produced by Mikos as modified, is designed to be a tissue counterpart to be used in the heart as a valve or portion thereof, and would reasonably have the structure and function of its tissue counterpart. According to the Examiner, such tissue would possess the properties of elasticity, flexibility and strength corresponding to the native tissue. Applicants respectfully disagree. It appears as though the Examiner is concluding that any engineered tissue necessarily has all the properties of the native tissue simply because it was intended to replace that tissue. If that were the case, the breakthrough in tissue engineered valves would not have been as late as 1995 (as stated in Mol and Schmidt), in view of the numerous attempts in the past and availability of tissue engineering tools well before 1995. As noted in Schmidt, many of the available heart valve prosthesis did not actively adapt to the physiological environment such as pressure changes and mechanical demands, because they remained inherently different from the tissue they replaced (see Schmidt, first page, left. col. 2nd para.). Therefore, one cannot conclude that simply because a structure is meant to replace a heart valve it would have all the properties of the heart valve, especially the ability to withstand pressure changes and mechanical demands (i.e. repeated stress and strain). Schmidt further discloses these limitations motivated the exploration of novel approaches towards valve replacement. Schmidt goes further to cite the studies by Shinoka (in 1995) as the first milestone in heart valve tissue engineering (see Schmidt, first page, right col. 2nd para.). There is nothing in any of Mikos, Sparks or Jauregui that would lead one of ordinary skill to this functional limitation i.e. a cell-matrix construct that can withstand repeated stress and strain-this is not an inherent characteristic of any and every device intended to replace a heart valve.

For at least the reasons set for the above, the claims are non-obvious over Mikos in view of Sparks and Jauregui.

Claims 12-14, 15/12, 15/13, and 15/14 are non-obvious over Mikos in view of Sparks or Jauregui and further in view of Griffith.

Claims 12-15 define a method for making a cell-matrix construct for use as a heart valve, with the limitations recited in claim 1. As discussed above, Mikos does not disclose all the elements of claim 1; none of Sparks or Jauregui to not make up for this deficiency. Similarly, Griffith does not make up for the efficiencies in Mikos. Therefore, the claims are non-obvious over the cited art.

Claims 1-8 and 8-15 are not obvious over Sparks in view of Mikos or Griffith-Cima and in view of either Jauregui or Tang.

The references cited by the Examiner do not disclose all of the claim limitations. Sparks does not disclose a method for making cell-matrix constructs for use as a heart valve as defined by claim 1. Sparks does not disclose or suggest using a fibrous polymeric matrix in the shape of a heart valve or heart valve leaflet which is implantable. Sparks does not disclose how to make a cell-matrix construct which can withstand repeated stress and strain. None of the secondary references make up for these deficiencies.

Sparks discloses a stainless steel die for growing a heart valve. A die cavity is formed between the outer and inner die members, and it is in this die cavity that the heart valve is grown (see Sparks, column 5, lines 18-20). A mesh reinforcing member is placed in the cavity, and connective tissue entering the die cavity through perforations in the outer die member encapsulates the mesh and completely fills the die cavity to form a heart valve which is similar in shape to the mesh. Thus the graft has a rigid circular base rim containing a steel ring (Sparks,

column 5, lines 32-40). It is clear from the disclosure in Sparks, that the method of forming the graft involves implanting a stainless steel die in an animal, containing DACRON™ mesh for reinforcement. Sparks does not teach that the fibrous matrix must be in the shape of a heart valve or heart leaflet.

The Examiner alleged that Sparks discloses a fibrous polymeric matrix in the shape of a heart valve, directing Applicants attention to Sparks, col. 5, lines 5-75. This is incorrect. Sparks discloses a stainless steel die for growing a tricuspid valve (col. 5, line 7), with holes through which connective tissue enters the die cavity encapsulating the mesh reinforcing member (51) **and completely fills the die cavity to form a heart valve graft (60) (shown in Figure 12), which is similar in shape to the reinforcing member** (51) (Sparks, col. 5, lines 32-36); the heart valve graft is similar in shape to the reinforcing member-the shape of the reinforcing member is not disclosed and "similar" is not characterized. The only polymeric material used in Sparks is DACRON™ mesh. The tissue is fibrotic, scar type tissue. It is similar to many of the materials used to form heart valves that last for a few years then have to be replaced. This is because they cannot handle the stress and strain of the tissue and do not integrate into the native organ.

There is no disclosure in Sparks that DACRON™ mesh is formed in the shape of a heart valve, nor can one of ordinary skill conclude that the disclosure in Sparks, of putting DACRON™ mesh (cloth) in the cavity formed between the stainless steel die pieces, is the same as forming a DACRON™ mesh in the shape of a heart valve. The Examiner also cited to Figure 7, which according to the Examiner, shows reinforcing mesh 51 approximating the shape of the die forming leaflets. This is not the same as the reinforcing mesh having the shape of a leaflet. The Examiner cannot separate the features disclosed in Sparks or read into Sparks' elements that

are not disclosed therein. The Examiner also alleged that Sparks at col. 5, lines 32-36 and 55-60 clearly teaches that the mesh has the same configuration as the die cavity. This is incorrect. Sparks at col. 5, lines 32-36 is discussed above- it discloses connective tissue enters the die cavity encapsulating the mesh reinforcing member (51) and completely fills the die cavity to form a heart valve graft (60) (shown in Figure 12), **which is similar in shape to the reinforcing member (51) –the valve graft is similar in shape to the dacron mesh, it is unclear from the cited section in Sparks, what that shape is.** Sparks at col. 5, lines 55-60 states "this (i.e., the three edges of valves retreating away when the valve is open) is also illustrated in Figure 9 wherein the upper edge portions (65) of the reinforcing mesh are shown in the same configuration they assume in the dies cavity, the latter having approximately the configuration assumed by the leaflets of the graft in the open position". This is not a disclosure of a DACRON™ mesh shaped in the form of the leaflets. Sparks discloses a method of forming a heart valve graft that involves implanting a perforated stainless steel die comprising a cavity within which the valve graft is formed by connective tissue entering the die cavity and encapsulating a DACRON™ mesh which approximates the configuration of the die cavity. This is different from the claimed method.

The Examiner relied on Mikos and Griffith-Cima or Tang for providing a biodegradable matrix. However, substituting the non-biodegradable DACRON™ mesh in Sparks with biodegradable polymers does not arrive at the claimed method for at least reasons stated above.

With respect to cell seeding, Sparks discloses that when a graft of epithelial tissue is desired, the die may be seeded with epithelial cells (column 4, lines 3-10). Sparks also states that before implanting a bone graft die, it is seeded with periosteal cells (column 4, lines 50-60). Further, Sparks does not disclose seeding any cells in valve grafts. Sparks is very clear when

cell seeding is required. Sparks is silent about seeding cells in valve grafts. Therefore, a *prima facie* case of obviousness has not been established, since the references (when combined) do not teach or suggest all the claim limitations.

There is no similarity whatsoever between the two methods. The only similarity between Sparks and the claims is the name of the resultant product. There is no similarity in the process of making, or the materials used, therefore it is expected that there would be no similar physical properties.

The Examiner cited to Mikos, alleging a disclosure by Vacanti 1, that the scaffold should mimic the natural tissue counterpart, and that Vacanti 1 provides evidence that better results are obtained when the matrix is first implanted, prevascularized and then seeded with select cell, attaching the relevant portion of Mikos (Mikos column 2, lines 16-44). Vacanti 1 is discussed above with respect to "mimicking the natural tissue counterpart". It is not clear what Mikos means by "better results" (cited by the Examiner); however, since Mikos is referring to Vacanti, the "better results" obtained are not concerned with a graft that can withstand repeated stress and strain, since Vacanti is only concerned with enhancing viability of large numbers of transplanted cells seeded onto an amorphous fibrous support structure (a gauze). It is clear from the discussion in Vacanti 1 that Vacanti 1 cannot make obvious the claimed method, which provides heart valves which can withstand repeated stress and strain. Vacanti does not recognize the problem with somehow providing the cell matrix with mechanical properties such as strength, flexibility, resistance to strain – features essential for a structure which will be opened, closed, and subjected to pressures every second, every hour, every day, every month, every year in the individual's life following implantation. There are simply no comparable requirements when it comes to a parenchymal tissue such as a liver or pancreas.

The Examiner also asserted that the materials used by Applicants are well known and known equivalents are taught by Jauregui or Tang, stating that Tang teaches that bioresorbable materials play a critical role in fabrication of devices used for tissue regeneration. The issue here is not merely using biodegradable materials to make heart valves. That biodegradable materials can be used in tissue engineering is known in the art, as correctly stated by the Examiner. It is also known that polymers can be molded to mimic the shape of the tissue to be engineered. However, making a structure with the requisite mechanical physical and mechanical properties necessary for biological function has been the challenge- see Mol and Schmidt.

The claims do not merely define a method that can be accomplished by substituting the DACRON™ Mesh in the stainless steel die of Sparks, with the biodegradable materials disclosed in Jauregui or Tang, or the use of the materials disclosed in Jauregui or Tang shaped into a three dimensional structure as suggested by Griffith and or Mikos. Claim 1 requires the cell-matrix be able to withstand repeated stress and strain; the claimed method steps arrive at a heart valve with this characteristic. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years.

However, according to the Examiner the device of Sparks as modified would inherently possess the properties that would be capable of withstanding cyclic stresses and strains, since the valve is designed to function as a replacement of a natural valve. The Examiner must provide a technical reason for a conclusion of inherency. According to the MPEP §2112 "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or

possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)". As demonstrated by Shinoka, et al. *Circulation*, 94(9 Suppl):II164-8 (1996) ("Shinoka 1", abstract attached to the amendment and response filed on May 8, 2007), the property of withstanding stress and strain is not inherent in biodegradable polymers, therefore merely replacing the DACRON™ mesh in Sparks with biodegradable polymers does not guarantee this characteristic. None of the cited references disclose that the biodegradable polymers necessarily possess the ability to withstand repeated stress and strain or how to adapt these polymers to have the requisite property. In fact, Shinoka 1 demonstrates this point.

With Respect to the Examiner's allegation that replacing the non-biodegradable mesh with a biodegradable mesh would eventually produce a tissue replacement having only natural confluent cells in the form of vascularized tissue which is essentially an equivalent counterpart to the natural tissue, and that it is a reasonable expectation that the tissue equivalent would possess the structure and function of its tissue counterpart, the Examiner's attention is drawn to the discussion of the disclosure in Mol and Schmidt above. As discussed in Mol and Schmidt, it has been the experience in the art that merely making a device to replace intricate structures such as heart valves does not necessarily impart to them all the functional characteristics of heart valves, absent specific steps taken to ensure the characteristic.

There is no motivation to combine the references as the Examiner has done, nor would it result in the claimed invention, much less do so predictably

There is no motivation to combine these references as the Examiner has done, nor would one skilled in the art have a reasonable expectation of success if one did so, based on the art, to yield a structure which can withstand repeated stress and strain. For example, Sparks describes

dies containing stainless steel, screws, and plates (see column 5, lines 18-31). This is completely different from the formation of tissue by injecting a cell-polymeric **solution** that gels *in vivo* (Griffith). As stated by the Examiner, Griffith teaches that the degradable template may be shaped or formed prior to implantation into the patient, and as such a combination of Griffith with Sparks would be impossible. Sparks needs the die to be implanted in order to shape the heart valve, Griffith teaches the implantation of a degradable hydrogel template with essentially no defined shape or structure and minimal mechanical properties. Not only is there no motivation to combine, there would be no reasonable expectation of success if one did so.

Mikos discloses preparing biocompatible porous polymer membranes by dispersing particles in a biocompatible polymer solution. There would be no motivation for one of ordinary skill in the art to replace the DACRON™ mesh with an absorbable matrix as taught by Mikos or Griffith, nor would one have a reasonable expectation that one could make a strong, flexible structure that could function has a heart valve or leaflet.

Jauregui discloses growing cells *on* a device that is to be implanted. Jauregui does not disclose seeding cells into a fibrous cell structure which is eventually replaced by the cells. Jauregui does not lead one skilled in the art to make a construct that is strong, flexible and useful as a heart valve. A skilled artisan would not be motivated to combine Jauregui and Sparks to arrive at the claimed method and construct, much less have a reasonable expectation of success. According to the MPEP §2143.01 "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the **desirability** of the combination".

Sparks does not disclose or suggest a method of making a cell-matrix construct for use as a heart valve comprising implanting into an animal a cell-matrix construct as recited in claim 1,

which is first cultured at a first site in a patient prior to being transplanted to a second site (claim 3). None of Mikos or Griffith or Jauregui makes up for this deficiency.

With respect to claim 8, claim 8 is dependent on claim 1, and recites the added limitation that the heart valve has mechanical strength, and flexibility or pliability. As already disclosed, Sparks does not disclose a method of making a heart valve as recited in claim 1, such that the valve has mechanical strength and flexibility or pliability. The Examiner asserts that the newly formed heart tissue would inherently possess the strength, flexibility and/or pliability of the tissue it is to replace. The Examiner has provided no technical reasoning for this conclusion and the literature rebuts such a conclusion. Without such a disclosure in Sparks, it would appear that the Examiner is concluding that because the graft is intended to replace heart valve, it would have all the characteristics of a heart valve. Please see Mol and Schimdt. It is clear from the disclosure in Mol and Schmidt that the mere fact that an object is intended to replace a biological structure does not inherently confer to the properties of that structure.

Conclusion

The art cited by the Examiner does not, either alone or in combination, recite all the elements of the claims as required by a rejection under 35 U.S.C 103(a). Even if they did, as the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. The Examiner has provided no reasoning why a person of ordinary skill in the art would combine the references as the Examiner has done. Therefore, the claims are non-obvious over the prior art.

Allowance of claims 1-5 and 8-15, is respectfully solicited.

Respectfully submitted,

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